Why Low Molecular Weight Heparin could not Gain the Confidence of Interventionists? An Overview

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Abstract: Presently coronary artery disease is considered as one of the major causes of mortality. The development of interventional cardiovascular technique such as coronary stenting has revolutionized the practice of interventional cardiology by overcoming partly some of the limitations of coronary angioplasty. During this procedure it produces vessel injury and induces thrombin generation and platelet activation with intertwined pathways, therefore Percutaneous Coronary Intervention (PCI) without anticoagulation appears unrealistic. It is almost universally accomplished with unfractionated heparin but the narrow risk-benefit ratio has led to search for better alternatives. The superiority of Low Molecular Weight Heparin (LMWH) over Un-Fractionated Heparin (UFH) is clear for ACS. Generally, the registries have reported a trend towards increased bleeding complications with LMWH than with UFH during PCI. In spite of its limitations, UFH proved to be the standard heparin therapy during PCI. This review study highlighted that LMWH requires further studies to determine their peri-catheterization monitoring, efficacy and safety profile.

Keywords: LMWH (Low molecular weight heparine), PCI (percutaneous coronary intervention), UFH (unfractionated heparine), ACT (activated clotting time)

INTRODUCTION

Coronary artery disease is commonly due to obstruction of the coronary arteries by atheromatous plaque (Masri, 1995). Despite steady progress in the treatment of cardiovascular disease, it still remains as one of the major causes of mortality (Fuster, 1999). By the year 2020, coronary heart disease and stroke will hold first and fourth places respectively, in the World Health Organization’s list of leading causes of disability (Murray and Lopez, 1997).

The main objective of therapy in patients with coronary artery disease is to alleviate symptoms of angina and reduce the risk of death or non-fatal myocardial infarction. Although, coronary angioplasty immediately reduces anginal symptoms in almost all the patients but its use is associated with death or nonfatal myocardial infarction in about 5% of patients and with restenosis requiring repeated angioplasty or bypass surgery in about 30% cases. The coronary stenting has revolutionized the practice of interventional cardiology by overcoming partially some of the limitations of coronary angioplasty, such as abrupt vessel closure due to coronary spasm, dissection or trauma, negative remodeling and to some extent restenosis (Bittl, 1996).

One of the major complications of coronary stenting is acute or sub-acute thrombotic occlusion within 24 h or within 2-14 days, respectively which occur in about four percent of patients after stent implantation and always results in myocardial infarction or death. Hence sub-acute thrombotic occlusion after stent implantation is the most serious problem (Wolf et al., 1995) and carries a high incidence of unfavorable clinical outcome, including mortality and acute myocardial infarction (Topol, 1994).

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Coronary stenting results in significant platelet activation and enhanced surface exposure of adhesion receptors on activated platelets and plays a key role in the development of subacute vessel closure after coronary intervention (Gawaz et al., 1996). Platelet activation follows adhesion and can be initiated by several mechanical and chemical stimuli. Adhesion of platelets to collagen and other components of the sub-endothelial matrix and the presence of thrombin are among the strongest stimulators of platelet activation. The activation of platelets is associated with stimulation of several metabolic pathways, changes in the shape of platelets, activation of the glycoprotein IIb/IIIa receptor and induction of platelet coagulant activity (Landau et al., 1994). Both cellular (platelets) and serologic (thrombin) factors play a central role in thrombotic process (Lefkovits et al., 1995). Percutaneous coronary intervention involves the peri-procedural use of antiplatelet agents and anticoagulants, where as the use of platelet inhibitors are relatively well established but it has been suggested that Aspirin may prevent ischemia reactivation following heparin discontinuation (Theroux et al., 1992). However, subsequent studies showed that reactivation can occur among patients receiving Aspirin (Thrombin Inhibition in Myocardial Ischemia (TRIM) study group, 1996).

Coller and his colleagues were the first to demonstrate that a murine monoclonal antibody directed against the glycoprotein IIb/IIIa receptor, inhibited the binding of fibrinogen to platelets and thus inhibited platelet aggregation (Coller et al., 1983).

Anticoagulation during Percutaneous Coronary Intervention (PCI) is almost universally accomplished with unfractionated heparin since the advent of Percutaneous Coronary Intervention (PCI), intravenous unfractionated heparin has been the primary anti-thrombotic therapy to prevent peri-procedural ischemic complications (Arjomand et al., 2002). The ACCP and the ACC/AHA/SCAI guidelines recommended that UFH should be administered to patients undergoing PCI (Smith et al., 1996) at a dose sufficient to produce an ACT of 250-350 sec, in patients receiving a GP IIb/IIIa inhibitor, a bolus dose of 50-70 IU kg⁻¹ of UFH to achieve an ACT of greater than 200 sec. Also, recommend weight-based dose of 60-100 IU kg⁻¹ and discourage routine post-procedural UFH infusion after uncomplicated PCI.

Un-Fractionated Heparin (UFH) is a glycosaminoglycan, composed of heterogeneous mixture of molecules of different weights, the anti-coagulation action of heparin is due to the binding of one-third of these molecules to anti-thrombin III, leading to a conformational change that markedly increases its ability to inactivate thrombin. The anticoagulant response to heparin varies greatly among patients. This may be due to different concentrations of heparin binding proteins and receptors on endothelial cells, which have to be saturated before a therapeutic plasma level can be achieved. Furthermore, natural inhibitors of heparin released from thrombus may decrease bioavailability of heparin (Hirsh et al., 2004). Moreover, thrombin is a potent direct activator of platelets and may consume antithrombin III which decreases availability for heparin to bind. Indeed a significant reduction in antithrombin activity may persist for 20 h or more, which is a vulnerable time for thrombus formation after unfractionated heparin for Percutaneous Coronary Intervention (PCI) reported by William et al. (1999). Increased level of both prothrombin fragment (free thrombin generation) and fibrinopeptide A thrombin activity have been observed after discontinuation of unfractionated heparin administered during Percutaneous Coronary Intervention (PCI) which may play role in rebound thrombosis after discontinuation (Smith et al., 1996).

It was also observed that unfractionated heparin directly activates platelet and enhances the response of platelets to low level of agonist Adenosine Diphosphate (Xiao and Theroux, 1998). This prothrombotic aspect of unfractionated heparin may have clinical consequences. For example, 33% of myocardial infarctions were observed following discontinuation of unfractionated heparin in GUSTO 1 trial within 10 h of unfractionated heparin discontinuation (Granger et al., 1996).

The clinical data in support of unfractionated heparin administration to patients with unstable angina is limited. In a meta-analysis of 1,353 patients from six trials, a marginal reduction in the
composite occurrence of death or myocardial infarction was observed over 2-7 days of unfractionated heparin therapy (Oler et al., 1996). The effect and dose of unfractionated heparin is being monitored during PCI by repeatedly performing Activated Clotting Time (ACT). The relationship of ACT to abrupt coronary closure is inverse and continuous (Nairns et al., 1996). While, the relationship to bleeding risk is direct and continuous (Hillegass et al., 1994).

Much of data in support of unfractionated heparin administration during PCI are nonrandomized and retrospective such as those reported by Ferguson et al. (1994), who noted that 80% of PCI procedures without complications had a procedural ACT of <300 sec. Eighty-five percent of those with complications had a procedural ACT of <250 sec. Hence, the optimal cut off for ACT during PCI was 300 sec. This retrospective study used Hemochrom technology to measure the ACT (Ferguson et al., 1995).

Interestingly, when the same blood sample is tested by other available technology for measuring ACT with Hemotec, the resultant ACT was 30% lower than that observed with Hemochrom. Thus, it is difficult to determine an optimal of ACT for a given technology during PCI (Ferguson et al., 1994).

Despite the widespread use of unfractionated heparin, the narrow risk-benefit ratio, has led to search for better alternatives. One such treatment has emerged through the depolymerization of unfractionated heparin to low molecular weight fragments (Harsh et al., 1995).

Low molecular weight heparin binds less avidly to plasma and tissue proteins than unfractionated heparin, has higher bioavailability and exerts more durable and predictable therapeutic effects. It has more pronounced effect on Factor Xa than on thrombin, so that its antithrombotic effect is not reflected by the activated partial thromboplastin time. Because of resistance to platelet factor 4, LMWH is more successful in attenuating thrombin generation even in the presence of activated platelets (Samama et al., 1994).

Low Molecular Weight Heparin (LMWH) in particular enoxaparin, has already been established as first line of choice for unstable angina and Non-ST-Elevation Myocardial Infarction (NSTEMI) stated by Braunwald et al. (2002). Increasing evidence suggested that LMWH may supersede unfractionated heparin in PCI and potentially replace it as the antithrombotic agent of choice across the whole spectrum of Acute Coronary Syndrome (ACS) reported by Wong et al. (2003). The use of LMWH before cardiac catheterization has been associated with favorable clinical outcomes in patients with UA/NSTEMI. Retrospective analysis of the ESSENCE and TIMI-IIIB trials suggested that the superior therapeutic effect of enoxaparin relative to unfractionated heparin is even more pronounced in patients who proceed to cardiac catheterization than those who are managed medically (Fox et al., 2000). As far as safety of LMWH enoxaparin is concerned, in both ESSENCE and TIMI-IIIB trials the patients receiving enoxaparin who underwent subsequent revascularization had rates of major bleeding similar to those seen in patients receiving unfractionated heparin. In these trials LMWH therapy was discontinued before catheterization and interventional procedures were performed using unfractionated heparin. More recent observational data suggests that once LMWH therapy has been initiated, it may be continued safely as a procedural anticoagulant, without switching to unfractionated heparin (Guzman et al., 1999).

Collet et al. (2001) evaluated the strategy of transition to PCI in 451 patients receiving standard enoxaparin therapy for UA/NSTEMI (1 mg kg\textsuperscript{-1} twice daily SC). Out of this, 132 patients underwent PCI with no additional bolus during the procedure. Twenty-five percent of these patients also received a GP IIb/IIIa inhibitors. There was no in-hospital abrupt coronary closure or urgent revascularization in any of the PCI patient, the incidence of death/MI at 30 days was 6.2% in the population as a whole and 3% in the PCI cohort. These observations are comparable favorably with those of previous studies. For example, in Abiximab plus low dose unfractionated heparin arm of EPILOG trial 1997 in which the lowest rates of both the major bleeding and ischemic events were observed. The incidence of death/MI at 30 days was 3.8%, the incidence of in-hospital major bleeding was 3.1%. The experience
of Collet et al. (2001) suggested that patients treated with standard dose of e诺xaparin subcutaneous in UA/NSTEMI may safely undergo PCI within 8 h of the last subcutaneous injection without additional anticoagulant (EPILOG Investigators, 1997).

Evidence exists that intravenous LMWH can be used as a procedural anticoagulant during cardiac catheterization with and without concurrent uses of GP IIb/IIIa inhibitors. Several recent observational studies and trials were performed using LMWH enoxaparin for patients undergoing PCI procedures, including the National Investigators Collaborating on Enoxaparin 2001 registry studies (NICE 1 and 4). In NICE 1, enoxaparin 1 mg kg\(^{-1}\) was given at the time of PCI without concurrent GP IIb/IIIa inhibitor. At 30 days major bleeding events occurred in 1.1% of patients, minor bleeding in 6.2%, death/mi or revascularization in 7.7%. In NICE 4 study a total of 818 patients received enoxaparin by standard dose 0.75 mg kg\(^{-1}\) intravenous with Abeiximab bolus and 12 h infusion 0.125 mg/kg/min to maximum of 10 mg/kg/min. At 30 days major bleeding occurred in o.4%, minor bleeding in 6.6%, death/MI or urgent revascularization in 8.8% (Kereiakes et al., 2001).

Cheussat et al. (2002) evaluated a lower dose of intravenous enoxaparin, 0.5 mg kg\(^{-1}\) bolus, in 242 patients undergoing elective PCI with clinical and safety outcomes comparable to those seen in other registries.

Superior yield of the new strategy of enoxaparin, revascularization and glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial showed that synergy is the largest trial to investigate LMWH in the catheterization setting and compared enoxaparin (1 mg kg\(^{-1}\) subcutaneously every 12 h) with UFH (60 IU kg\(^{-1}\) IV bolus followed by 12 IU/kg/h) in 10,027 high-risk ACS patients intended to receive primary PCI. The end point of death (3.2 with enoxaparin vs. 3.1 with UFH) or MI (11.7 with enoxaparin vs. 12.7 with UFH) at 30 days resulted in no significant differences. Of note, Thrombolytics in Myocardial Infarction (TIMI) major bleeding rates (9.1% with enoxaparin vs. 7.6% with UFH, \(p = 0.008\)) and Coronary Artery Bypass Graft (CABG)-related hemorrhage rates (6.8% with enoxaparin vs. 5.9% with UFH, \(p = 0.08\) were higher in patients randomized to receive enoxaparin. Investigators concluded that enoxaparin was a safe and effective alternative to UFH and that the benefits of the agent should be balanced with the modest increase in bleeding risk (Ferguson et al., 2004).

Similarly, the recently completed STEEPLE trial in late 2005 compared the safety of enoxaparin with that of UFH in non emergent PCI. The patients receiving enoxaparin 0.5 mg kg\(^{-1}\) and enoxaparin 0.75 mg kg\(^{-1}\) had significantly lower rates of major bleeding compared with UFH (0.9% vs 2.6%, \(p = 0.004\) and 1.2% vs 2.6%, \(p = 0.015\), respectively) and investigators concluded that enoxaparin is a safe and effective alternative to UFH in elective PCI (Steeple, 2005).

The ExTRACT-TIMI 25 trial, of which the results were announced at the 2006 ACC Scientific Session, compared the safety and efficacy of enoxaparin to UFH in STEMI patients with or without PCI and found enoxaparin superior to UFH for 48 h, but with an increase in major bleeding. The primary efficacy end point of death or non-fatal recurrent MI through 30 days of randomization occurred in 12% of patients treated with UFH and in 9% of patients treated with enoxaparin. This resulted in a 17% relative risk reduction in patients treated with enoxaparin (\(p<0.001\)). The primary safety end point of major, minor and minimal bleeding resulted in higher rates of major bleeding in patients treated with enoxaparin compared to UFH (2.1% vs 1.4%\(p<0.001\)), respectively (Antman et al., 2006).

In order to minimize thromboembolic events, the use of effective and safe anticoagulation therapy is needed during PCI although the optimal dose of Unfractionated Heparin (UFH), the most commonly used anticoagulant during PCI, remains unknown (Kokolis et al., 2004) but at the start of PCI, a 50-100 U/I kg\(^{-1}\) bolus of UFH is now recommended. If GP IIb/IIIa inhibitors are given, the use of low doses of UFH (50-70 UI kg\(^{-1}\)) limits the bleeding complications (EPILOG Investigators, 1997). Also, weight-adjusted low doses appear at least as safe as fixed high doses (Boocara et al., 1997).
the fact that UFH is considered the gold standard of antithrombin therapy in PCI there are some disadvantages. The potential advantages of LMWH over UFH include its greater affinity for Factor Xa, a reduced likelihood of protein and cellular binding (i.e., a more predictable dose response), relative absence of thrombin rebound, lack of sensitivity to PF4 and a lower incidence of thrombocytopenia (Choo and Kereteakis, 2001). The superiority of LMWH over UFH is clear for ACS. But there is a trend towards increased bleeding complications during PCI with LMWH than with UFH (Choussat et al., 2002; Ferguson et al., 2004; Steeple, 2005; Antman et al., 2006). LMWH being novel agent need more time to be tested in the cath laboratories and require more studies to determine their peri-catheterization (or it should be pre-catheterization) monitoring, efficacy and safety profile. However in my view point, this modality of anticoagulation will gain the confidence of interventional cardiologists being more effective and simple in the years to come.

REFERENCES


